

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 03/082295 A1

(51) International Patent Classification⁷: **A61K 31/5377**,
A61P 29/00, 11/06, C07D 413/12, 413/06, 209/48, 265/30

(21) International Application Number: PCT/EP03/03349

(22) International Filing Date: 27 March 2003 (27.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0207439.1 28 March 2002 (28.03.2002) GB

(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ANCLIFF, Rachael, Ann** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **COOK, Caroline, Mary** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **ELDRED, Colin, David** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **GORE, Paul, Martin** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **HARRISON, Lee, Andrew** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **HAYES, Martin, Alistair** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **HODGSON, Simon, Teanby** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **JUDD, Duncan, Bruce** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **KEELING, Suzanne, Elaine** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **LEWELL, Xiao, Qing** [GB/GB]; GlaxoSmithKline,

Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **MILLS, Gail** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **ROBERTSON, Graeme, Michael** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **SWANSON, Stephen** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **WALKER, Andrew, John** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **WILKINSON, Mark** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: **GIDDINGS, Peter, John**; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

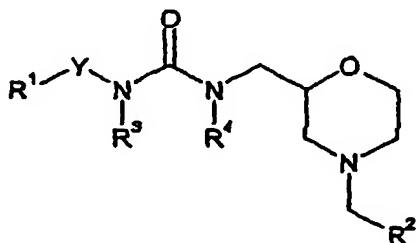
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MORPHOLINE DERIVATIVES SUBSTITUTED AT THE 2-POSITION BY A HETEROCYCLYLALKYLUREA GROUP FOR USE AS CCR-3 ANTAGONISTS IN THE TREATMENT OF INFLAMMATORY CONDITIONS



(I)

(57) Abstract: Certain compounds of formula (I): wherein: R¹ represents substituted or unsubstituted heterocyclyl; Y represents -(CR_{na}R_{nb})_n-; R_{na} and R_{nb} are each independently hydrogen or C₁₋₆ alkyl; n is an integer from 1 to 5; R² represents unsubstituted or substituted aryl or unsubstituted or substituted, heteroaryl; R³ and R⁴ each independently represent hydrogen or C₁₋₆ alkyl; and salts and solvates thereof are CCR-3 antagonists and thus are indicated to be useful in therapy of inflammatory conditions.

MORPHOLINE DERIVATIVES SUBSTITUTED AT THE 2-POSITION BY A HETEROCYCLYLALKYLUREA GROUP FOR USE AS CCR-3 ANTAGONISTS IN THE TREATMENT OF INFLAMMATORY CONDITIONS

Novel Compounds

This invention relates to novel compounds, processes for their preparation, pharmaceutical formulations containing them and their use in therapy.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by leukocyte adhesion to the endothelium, diapedesis and activation within the tissue. Leukocyte activation can result in the generation of toxic oxygen species (such as superoxide anion), and the release of granule products (such as peroxidases and proteases). Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by the profile of adhesion molecule, cytokine and chemotactic factor expression within the tissue.

The primary function of leukocytes is to defend the host from invading organisms, such as bacteria and parasites. Once a tissue is injured or infected, a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, recruitment is often inappropriate, resolution is not adequately controlled and the inflammatory reaction causes tissue destruction.

There is increasing evidence that the bronchial inflammation which is characteristic of asthma represents a specialised form of cell-mediated immunity, in which cytokine products, such as IL-4 and IL-5 released by T-helper 2 (Th2) lymphocytes, orchestrate the accumulation and activation of granulocytes, in particular eosinophils and to a lesser extent basophils. Through the release of cytotoxic basic proteins, pro-inflammatory mediators and oxygen radicals, eosinophils generate mucosal damage and initiate mechanisms that underlie bronchial hyperreactivity. Therefore, blocking the recruitment and activation of Th2 cells and eosinophils is likely to have anti-inflammatory properties in asthma. In addition, eosinophils have been implicated in other disease types such as rhinitis, eczema, irritable bowel syndrome and parasitic infections.

Chemokines are a large family of small proteins which are involved in trafficking and recruitment of leukocytes (for review see Luster, New Eng. J. Med., 338, 436-445 (1998)). They are released by a wide variety of cells and act to attract and activate various cell types, including eosinophils, basophils, neutrophils, macrophages, T and B lymphocytes. There are two major families of chemokines, CXC- (α) and CC- (β) chemokines, classified according to the spacing of two conserved cysteine residues near to the amino terminus of the

chemokine proteins. Chemokines bind to specific cell surface receptors belonging to the family of G-protein-coupled seven transmembrane-domain proteins (for review see Luster, 1998). Activation of chemokine receptors results in, amongst other responses, an increase in intracellular calcium, changes in cell shape, increased expression of cellular adhesion molecules, degranulation and promotion of cell migration (chemotaxis).

To date a number of CC chemokine receptors have been identified and of particular importance to the current invention is the CC-chemokine receptor-3 (CCR-3), which is predominantly expressed on eosinophils, and also on basophils, mast cells and Th2 cells. Chemokines that act at CCR-3, such as RANTES, MCP-3 and MCP-4, are known to recruit and activate eosinophils. Of particular interest are eotaxin and eotaxin-2, which specifically bind to CCR-3. The localization and function of CCR-3 chemokines indicate that they play a central role in the development of allergic diseases such as asthma. Thus, CCR-3 is specifically expressed on all the major cell types involved in inflammatory allergic responses. Chemokines that act at CCR-3 are generated in response to inflammatory stimuli and act to recruit these cell types to sites of inflammation, where they cause their activation (e.g. Griffiths et al., J. Exp. Med., 179, 881-887 (1994), Lloyd et al., J. Exp. Med., 191, 265-273 (2000)). In addition, anti-CCR-3 monoclonal antibodies completely inhibit eotaxin interaction with eosinophils (Heath, H. *et al.*, J. Clin. Invest. 99 (2), 178-184 (1997)), while an antibody for the CCR-3 specific chemokine, eotaxin, reduced both bronchial hyperreactivity and lung eosinophilia in an animal model of asthma (Gonzalo et al., J. Exp. Med., 188, 157-167 (1998)). Thus, many lines of evidence indicate that antagonists at the CCR-3 receptor are very likely to be of therapeutic use for the treatment of a range of inflammatory conditions.

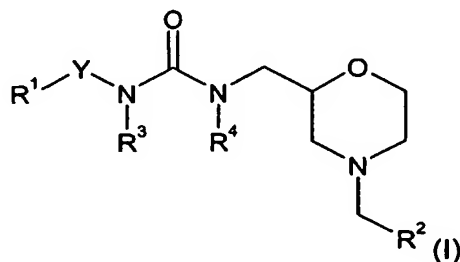
In addition to a key role in inflammatory disorders, chemokines and their receptors also play a role in infectious disease. Mammalian cytomegaloviruses, herpes viruses and pox viruses express chemokine receptor homologues, which can be activated by human CC chemokines such as RANTES and MCP-3 receptors (for review see Wells and Schwartz, Curr. Opin. Biotech., 8, 741-748, 1997). In addition, human chemokine receptors, such as CXCR-4, CCR-5 and CCR-3, can act as co-receptors for the infection of mammalian cells by microbes such as human immunodeficiency viruses (HIV). Thus, chemokine receptor antagonists, including CCR-3 antagonists, may be useful in blocking infection of CCR-3 expressing cells by HIV or in preventing the manipulation of immune cellular responses by viruses such as cytomegaloviruses.

International Patent Application publication number WO 01/24786 (Shionogi & Co. Ltd.) discloses certain aryl and heteroaryl derivatives for treating diabetes. WO 00/69830 (Torrey Pines Institute for Molecular Studies) discloses certain

diazacyclic compounds, and libraries containing them, for biological screening. WO 00/18767 (Neurogen Corporation) discloses certain piperazine derivatives as dopamine D4 receptor antagonists. United States Patent 6,031,097 and WO 99/21848 (Neurogen Corporation) discloses certain aminoisoquinoline derivatives as dopamine receptor ligands. WO 99/06384 (Recordati Industria Chimica) discloses piperazine derivatives useful for the treatment of neuromuscular dysfunction of the lower urinary tract. WO 98/56771 (Schering Aktiengesellschaft) discloses certain piperazine derivatives as anti-inflammatory agents. WO 97/47601 (Yoshitomi Pharmaceutical Industries Ltd.) discloses certain fused heterocyclic compounds as dopamine D-receptor blocking agents. WO 96/39386 (Schering Corporation) discloses certain piperidine derivatives as neurokinin antagonists. WO 96/02534 (Byk Gulden Lomberg Chemische Fabrik GmbH) discloses certain piperazine thiopyridines useful for controlling helicobacter bacteria. WO 95/32196 (Merck Sharp & Dohme Limited) discloses certain piperazine, piperidine, and tetrahydropyridine derivatives as 5-HT1D- α antagonists. United States Patent 5,389,635 (E.I. Du Pont de Nemours and Company) discloses certain substituted imadazoles as angiotensin-II antagonists. European Patent Application publication number 0 306 440 (Schering Aktiengesellschaft) discloses certain imidazole derivatives as cardiovascular agents.

A novel group of compounds has now been found which are CCR-3 antagonists. These compounds block the migration/chemotaxis of eosinophils and thus possess anti-inflammatory properties. These compounds are therefore of potential therapeutic benefit, especially in providing protection from eosinophil, basophil mast cell and Th2-cell-induced tissue damage in diseases where such cell types are implicated, particularly allergic diseases, including but not limited to bronchial asthma, allergic rhinitis and atopic dermatitis.

Thus, according to one aspect of the invention, there are provided compounds of formula (I):



wherein:

R¹ represents substituted or unsubstituted heterocyclyl;

Y represents $-(CR_{na}R_{nb})_n$;

R_{na} and R_{nb} are each independently hydrogen or C_{1-6} alkyl;

n is an integer from 1 to 5;

R^2 represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;

R^3 and R^4 each independently represent hydrogen or C_{1-6} alkyl;
and salts and solvates thereof;

with the proviso that the following compounds are excluded;

N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-[2-(2-oxoimidazolidin-1-yl)ethyl]urea;

tert-butyl 4-([4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl)amino}carbonyl]amino}methyl)piperidine-1-carboxylate;

N-[[1-(cyclopropylcarbonyl)piperidin-4-yl]methyl]-N'-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea, and;

N-[[1-(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-{[1-(methylsulfonyl)piperidin-4-yl]methyl}urea.

Examples of the heterocyclyl group, R^1 , include piperidinyl.

When R^1 is substituted heterocyclyl, suitable substituents include C_{3-8} cycloalkylaminocarbonyl, C_{1-6} alkylcarbonyl, aminocarbonyl, C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, mono- and di- $(C_{1-6}$ alkyl)aminocarbonyl, C_{1-6} alkylsulphonyl, and C_{1-6} alkoxy C_{1-6} alkyl.

Suitably, R^1 is unsubstituted or substituted piperidinyl.

When R^1 is selected from substituted piperidinyl, suitable substituents include C_{3-8} cycloalkylaminocarbonyl, mono- and di- $(C_{1-6}$ alkyl)aminocarbonyl; C_{1-6} alkoxycarbonyl, and aminocarbonyl.

More suitably, R^1 is selected from 1-(methylaminocarbonyl)piperidin-4-yl, 1-(diethylaminocarbonyl)piperidin-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 1-(cyclopropylaminocarbonyl)piperidin-4-yl, 1-(ethylaminocarbonyl)piperidin-4-yl, 1-(iso-propylaminocarbonyl)piperidin-4-yl, 1-(ethoxycarbonyl)piperidin-4-yl, 1-(tert-butoxycarbonyl)piperidin-4-yl and 1-(aminocarbonyl)piperidin-4-yl.

Suitably, R_{na} and R_{nb} are both hydrogen.

Suitably, n is 1.

Suitably, R^3 and R^4 are both hydrogen.

When R^2 is aryl, examples include phenyl.

When R^2 is substituted aryl, suitable substituents include cyano, perhalo C_{1-6} alkyl, amido, halo, C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, mono- and di- $(C_{1-6}$ alkyl)aminocarbonyl, C_{1-6} alkoxy, nitro, C_{1-6} alkylsulphonyl, hydroxy, C_{1-6} alkoxy C_{1-6} alkyl, C_{1-6} alkylthio, mono- and di- $(C_{1-6}$ alkyl)amino, and C_{1-6} alkylcarbonylamino.

When R^2 is heteroaryl, examples include thiophenyl.

When R^2 is substituted heteroaryl, suitable substituents include cyano, perhalo C_{1-6} alkyl, amido, halo, C_{1-6} alkyl, C_{1-6} alkoxycarbonyl, mono- and di- $(C_{1-6}$ alkyl)aminocarbonyl, C_{1-6} alkoxy, nitro, C_{1-6} alkylsulphonyl, hydroxy, C_{1-6} alkoxy C_{1-6} alkyl, C_{1-6} alkylthio, mono- and di- $(C_{1-6}$ alkyl)amino, and C_{1-6} alkylcarbonylamino.

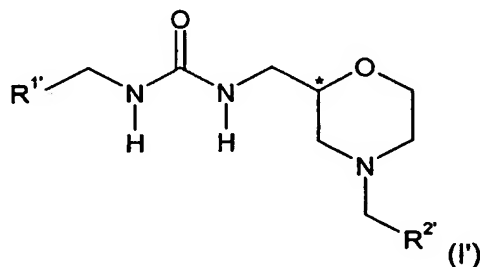
Suitably, R^2 is unsubstituted or substituted phenyl.

When R^2 is substituted phenyl suitable substituents include halo.

More suitably, R^2 is phenyl substituted with chloro.

Preferably, R^2 is 3,4-dichlorophenyl.

There exists a preferred subgroup of compounds of formula (I) being of formula (I')



wherein:

R^1 is unsubstituted or substituted heterocyclyl, and;

R^2 is phenyl substituted with halo.

Examples of the heterocyclyl group, R^1 , include piperidinyl.

Suitably, R^1 is piperidin-4-yl substituted with mono- or di- $(C_{1-6}$ alkyl)aminocarbonyl, C_{1-6} alkoxycarbonyl, C_{3-8} cycloalkylaminocarbonyl, or aminocarbonyl.

Preferably, R^1 is 1-(methylaminocarbonyl)piperidin-4-yl, 1-(diethylaminocarbonyl)piperidin-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 1-(cyclopropylaminocarbonyl)piperidin-4-yl, 1-(ethylaminocarbonyl)piperidin-4-yl, 1-(iso-propylaminocarbonyl)piperidin-4-yl, 1-(ethoxycarbonyl)piperidin-4-yl, 1-(tert-butoxycarbonyl)piperidin-4-yl or 1-(aminocarbonyl)piperidin-4-yl.

Suitably, R^2 is phenyl substituted with chloro or fluoro.

Preferably, R^2 is 3,4-dichlorophenyl.

Suitably, the stereochemistry at the position marked '*' is (S).

Accordingly, there is provided a compound of formula (I') or a salt or solvate thereof.

Suitable compounds of the invention are Examples 1, 2, 3, 6, 4, 5, 7, and 8.

Preferred compounds of the invention are Examples 1, 2, and 3.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, palmoates, methanesulphonates, formates or trifluoroacetates.

Examples of solvates include hydrates.

Certain of the compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the stereoisomers of the compounds of formula (I), including geometric isomers and optical isomers, whether as individual stereoisomers or as mixtures thereof including racemic modifications.

Generally it is preferred that a compound of formula (I) is in the form of a single enantiomer or diastereoisomer.

Certain of the compounds of formula (I) may exist in one of several tautomeric forms. It will be understood that the present invention encompasses all of the tautomers of the compounds of formula (I) whether as individual tautomers or as mixtures thereof.

References to 'aryl' refer to monocyclic and bicyclic carbocyclic aromatic rings, for example naphthyl and phenyl, especially phenyl.

Suitable substituents for any aryl group include 1 to 5, suitably 1 to 3, substituents selected from the list consisting of cyano, perhaloalkyl, amido, halo, alkyl, alkoxycarbonyl, mono- and di-(alkyl)aminocarbonyl, alkoxy, nitro, alkylsulphonyl, hydroxy, alkoxyalkyl, alkylthio, mono- and di-(alkyl)amino, and alkylcarbonylamino.

References to 'heteroaryl' refer to monocyclic heterocyclic aromatic rings containing 1-4 heteroatoms selected from nitrogen, oxygen and sulphur. Examples of heterocyclic aromatic rings include thiophenyl.

Suitable substituents for any heteroaryl group include 1 to 5, suitably 1 to 3, substituents selected from the list consisting of cyano, perhaloalkyl, amido, halo, alkyl, alkoxycarbonyl, mono- and di-(alkyl)aminocarbonyl, alkoxy, nitro, alkylsulphonyl, hydroxy, alkoxyalkyl, alkylthio, mono- and di-(alkyl)amino, and alkylcarbonylamino.

References to 'alkyl' refer to both straight chain and branched chain aliphatic isomers of the corresponding alkyl, suitably containing up to six carbon atoms.

References to 'cycloalkyl' refer to saturated alicyclic rings suitably containing 3-8 carbon atoms.

Suitable substituents for any cycloalkyl group include alkyl, halo, and hydroxy.

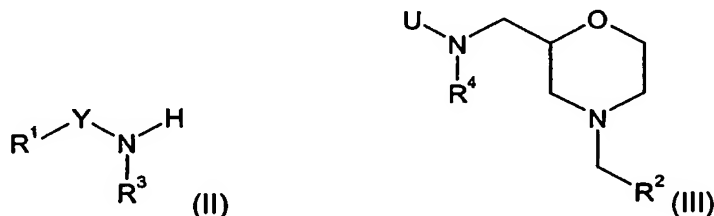
References to 'heterocyclyl' refer to monocyclic heterocyclic aliphatic rings containing 2 to 6, suitably 3 to 5, carbon atoms, and 1 to 3, heteroatoms selected from nitrogen, oxygen, and sulphur. Examples of heterocyclic rings include piperidinyl.

Suitable substituents for any heterocyclyl group include cycloalkylaminocarbonyl, alkylcarbonyl, aminocarbonyl, alkyl, alkoxy carbonyl, mono- and di-(alkyl)aminocarbonyl, alkylsulphonyl, and alkoxyalkyl.

References to 'halogen' or 'halo' refer to iodo, bromo, chloro or fluoro, especially chloro.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

Accordingly, there is provided a process for the preparation of a compound of formula (I) which process comprises the reaction of a compound of formula (II) with a compound of formula (III);



wherein;

R^1 , Y, R^3 , R^4 , and R^2 are as hereinbefore defined for formula (I) and U is a urea-forming group;

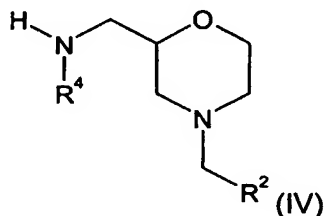
and thereafter, if required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) removing any necessary protecting group;
- (iii) preparing a salt or solvate of the compound so formed.

A urea-forming group is a group which is derived from a reagent which introduces a carbonyl group and a leaving group to an amino compound. Examples of urea-forming groups are imidazolylcarbonyl and chlorocarbonyl, and, when R^4 is hydrogen, then 4-nitrophenoxy carbonyl may be used. The reagents from which they are derived are 1,1'-carbonyldiimidazole, phosgene, and 4-nitrophenylchloroformate respectively. A suitable urea-forming group is 4-nitrophenoxy carbonyl.

Typically, the compound of formula (II) and the compound of formula (III) in a suitable solvent, such as an organic solvent, e.g. dichloromethane are treated with a suitable base, such as a tertiary amine, e.g. triethylamine, at ambient temperature, such as 18 - 25°C.

A compound of formula (III) may be prepared by reaction of a compound of formula (IV);



wherein;

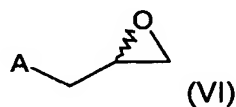
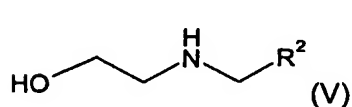
R^4 and R^2 are as hereinbefore defined for formula (I);

with a compound of formula U-L wherein U is a urea-forming group as hereinbefore defined and L is a leaving group. A suitable leaving group is a halo group such as chloro.

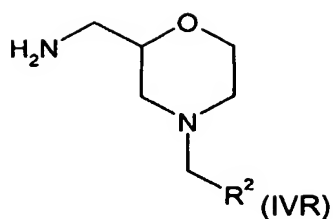
The reaction between the compound of formula (IV) in the presence of a suitable base, such as a tertiary amine, e.g. triethylamine, and the compound U-L is performed in a suitable solvent, for example dichloromethane, at a suitable temperature, for example those in the range of -5°C to +5°C over a suitable period of time, for example 3-5 hours. Conventional methods of cooling may be employed, for example ice/salt baths. The product is isolated by conventional means, such as washing with brine, drying with a suitable drying agent such as magnesium sulphate, followed by concentration *in vacuo*.

A compound of formula (IV) wherein R^4 is hydrogen may be prepared either by Reaction (a) or Reaction (c). The S-enantiomer of a compound of formula (IV) may be prepared by Reaction (b).

Reaction (a). Reaction of the compound of formula (V) with a compound of formula (VI)



wherein R^2 is as hereinbefore defined for formula (I) and A is a protected amino group, suitably phthalimido, followed by deprotection of the amino group to give a compound of formula (IV) wherein R^4 is hydrogen i.e. a compound of formula (IVR)



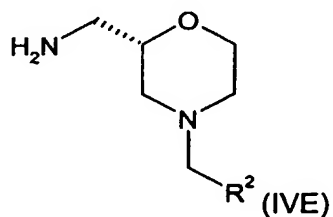
wherein R^2 is as hereinbefore defined, and optionally resolution of the resulting enantiomers of a compound of formula (IVR);

or;

Reaction (b). Reaction of a compound of formula (V) as hereinbefore defined with a compound of formula (VIA)

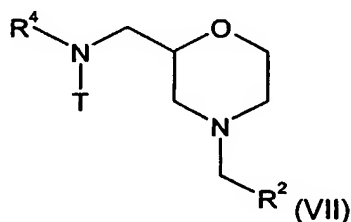


wherein A is as hereinbefore defined for formula (VI), followed by deprotection of the amino group to give the corresponding enantiomer of a compound of formula (IV) wherein R^4 is hydrogen i.e. a compound of formula (IVE)



wherein R^2 is as hereinbefore defined.

Reaction (c). Hydrolysis of a compound of formula (VII);



wherein T is trifluoroacetyl, and R^4 and R^2 are as hereinbefore defined for formula (I), and optionally resolution of the resulting enantiomers of a compound of formula (IV).

For both reactions (a) and (b), the reaction between the compound of formula (V) and a compound of formula (VI) or (VIA) is typically carried out under the Mitsunobu conditions as follows:

Typically, a mixture of the compound of formula (V) and the compound of formula (VI) or formula (VIA) in a suitable solvent, such as tetrahydrofuran, is stirred, suitably for 20 - 24 hours at a suitable temperature, suitably the reflux temperature of the solvent, under an inert atmosphere, suitably an atmosphere of nitrogen. Further solvent is then added and the mixture cooled, suitably to 0-5°C. A suitable phosphine, suitably triphenyl phosphine, is added and the mixture stirred until all the solid is dissolved. A suitable azo compound, suitably diisopropylazodicarboxylate, is then added over a period of time, suitably, 10 -15 minutes, while maintaining the temperature at <7°C. The mixture is allowed to stand for a period of time, suitably 2 - 3 hours, then allowed to warm, suitably to 20 - 25°C. After a further period of standing, suitably 4 - 6 hours, further phosphine and azo compounds are added. After a further period of standing, suitably 20 -24 hours, the reaction mixture is concentrated to near dryness. A suitable alcohol, suitably propan-2-ol, is added and the concentration step repeated; the alcohol addition and concentration step is then repeated. Further alcohol is then added and the mixture heated to a temperature suitably between 65 - 75°C. After a suitable period, suitably 20 - 45 minutes, the resultant slurry is cooled, suitably to 20 - 25°C, and then allowed to stand, suitably for 1.5 - 3 hours, after which time the product is isolated by filtration. The filter bed is washed with more alcohol and then dried *in vacuo* at 35 - 45°C to yield the protected form of the compound of formula (IVR) or formula (IVE) respectively.

The removal of the protecting group from the product is typically carried out as follows. A slurry of the protected form of the compound of formula (IVR) or formula (IVE) in an appropriate polar solvent, suitably water, is heated to elevated temperature, suitably 70 - 75°C and then treated dropwise with a concentrated mineral acid, suitably concentrated sulphuric acid. The mixture is then heated at elevated temperature, suitably the reflux temperature of the solvent, for a suitable period of time, suitably 20 - 24 hours, after which the reaction mixture is cooled to 20 - 25°C and then treated with a suitable apolar solvent, suitably dichloromethane. A base, suitably 0.880 ammonia solution, is then added dropwise, maintaining the temperature between 20 - 25°C. Further apolar solvent is then added, the aqueous phase then being separated and extracted with further apolar solvent. The combined organic phase is washed with water and then evaporated to dryness. The residue is redissolved and the apolar solvent re-evaporated to give the compound of formula (IVR) or formula (IVE).

The process for the preparation of the protected form of the compound of formula (IVR) or formula (IVE) described above may also be undertaken in two stages, in which an intermediate compound of formula (IVBR) or of formula (IVBE) respectively;



wherein A is as hereinbefore defined for formulae (VI) and (VIA) and R² is as hereinbefore defined for formula (I); is isolated.

Typically, a mixture of the compound of formula (V) and a compound of formula (VI) or formula (VIA) in a suitable solvent, such as tetrahydrofuran, is stirred, suitably for 20-24 hours at a suitable temperature, suitably the reflux temperature of the solvent, under an inert atmosphere, suitably an atmosphere of nitrogen. Further compound of formula (V) is added and the mixture heated at a suitable temperature, suitably the reflux temperature of the solvent, under an inert atmosphere, suitably an atmosphere of nitrogen, for a suitable period of time, suitably 3-6 hours. The reaction mixture is then cooled, suitably to 20-25°C, and the compound precipitated by means of addition of a suitable co-solvent, suitably diisopropyl ether. The compound of formula (IVBR) or formula (IVBE) respectively is isolated by filtration, washed with further co-solvent and dried *in vacuo*.

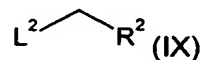
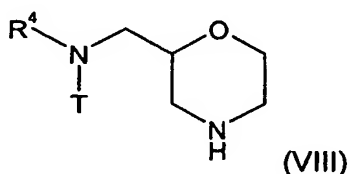
A protected form of the compound of formula (IVR) or formula (IVE) may then be prepared from a compound of formula (IVBR) or formula (IVBE) under similar conditions to those of the reaction between a compound of formula (V) and formulae (VI) or (VIA) as hereinbefore described, but omitting the reflux period prior to the addition of the phosphine and azo compounds.

Reaction (c) is typically carried out by stirring a solution of the compound of formula (VII) in a suitable solvent, for example a mixture of methanol and water, and adding a suitable base, for example potassium carbonate. The mixture is stirred at a suitable temperature, for example those in the range 20-25°C for a suitable time, for example 16-20 hours followed by removal of the organic solvent *in vacuo*. Water is then added and the mixture extracted with a suitable organic solvent, for example ethyl acetate. The combined organic phases are washed with water and saturated aqueous sodium chloride solution before drying over a suitable drying agent, for example sodium sulphate, filtering

and evaporation of the solvent in vacuo. The crude product is then purified by flash chromatography.

The resolution of the compound of formula (IVE) from the racemic product i.e. the compound of formula (IVR) may be undertaken using techniques well known to those skilled in the art, for example preparative chiral high performance liquid chromatography (chiral HPLC) or by fractional crystallisation of diastereoisomeric salts.

A compound of formula (VII) may be prepared by reaction of a compound of formula (VIII) with a compound of formula (IX)

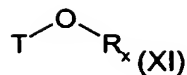
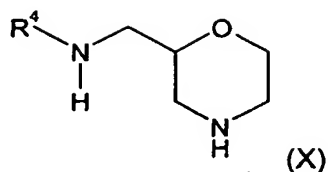


wherein;

T, R⁴ and R² are as hereinbefore defined for formula (VII) and L² is a leaving group. A suitable leaving group, L² is a halo group such as chloro.

The reaction between a compound of formula (VIII) and a compound of formula (IX) is typically carried out by stirring a solution of the compound of formula (VIII) in a suitable solvent, for example N,N-dimethylformamide, under an inert atmosphere, for example an atmosphere of nitrogen, with the addition of a suitable base, for example potassium carbonate, and a suitable activating agent, such as sodium iodide. A solution of a compound of formula (IX) in a suitable solvent, such as N,N-dimethylformamide, is added dropwise to the mixture. The mixture is then stirred at a suitable temperature, for example a temperature in the range of 20-25°C, for a suitable period of time, for example 16-20 hours before removing the volatile components in vacuo. The residue is partitioned between a suitable organic solvent, for example dichloromethane, and a saturated aqueous base, for example saturated aqueous sodium carbonate solution. The organic phase is then washed with additional saturated aqueous base and water before drying over a suitable drying agent, for example magnesium sulphate, filtering and evaporation of the solvent in vacuo to yield the crude product. The crude product is purified by flash chromatography.

A compound of formula (VIII) may be prepared by reaction of a compound of formula (X) with a compound of formula (XI);



wherein R^4 and T are as hereinbefore defined for formula (VII) and R_x is an alkyl group, suitably ethyl.

The reaction between a compound of formula (X) and a compound of formula (XI) is typically carried out by stirring a solution of a compound of formula (X) in a suitable organic solvent, for example methanol, under an inert atmosphere, for example an atmosphere of nitrogen, and then adding a solution of a compound of formula (XI) in a suitable organic solvent, for example ether. The mixture is then stirred for a suitable period of time, for example 20-40 minutes at a suitable temperature, for example a temperature in the range of 20-25°C and the volatile components removed in vacuo. The residue is then dissolved in a suitable organic solvent, for example methanol, and the volatile components removed in vacuo.

The compounds of formulae (II), certain compounds of formula (IV), certain compounds of formula (V), (VI), certain compounds of formula (VII), certain compounds of formula (VIII), (IX), (X), and (XI) are known, commercially available compounds, and/or may be prepared by analogy with known procedures, for examples those disclosed in standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience*.

The compounds of formulae (III), (IVBR), and (IVBE) are considered to be novel.

Accordingly, there is provided compounds of formula (III).

There is also provided a compound of formula (IVBR).

There is also provided a compound of formula (IVBE).

The above mentioned conversion of a compound of formula (I) into another compound of formula (I) includes any conversion which may be effected using conventional procedures, but in particular the said conversions include converting one group R^1 into another group R^1 .

The above mentioned conversion may be carried out using any appropriate method under conditions determined by the particular groups chosen. Thus, suitable conversions of one group R^1 into another group R^1 include:

(a) converting a group R^1 which represents a heterocyclyl group substituted with an alkoxy carbonyl group into a group R^1 which represents an unsubstituted heterocyclyl group; such a conversion may be carried out using an appropriate

- conventional deprotection procedure, for example hydrolysing an appropriately protected compound of formula (I) with a suitable mineral acid;
- (b) converting a group R^1 which represents an unsubstituted heterocyclyl group into a group R^1 which represents a heterocyclyl group substituted with an alkylaminocarbonyl group; such a conversion may be carried out using an appropriate conventional urea-forming procedure, for example treating an appropriately protected compound of formula (I) with a suitable isocyanate;
- (c) converting a group R^1 which represents an unsubstituted heterocyclyl group into a group R^1 which represents a heterocyclyl group substituted with an alkoxy carbonyl group; such a conversion may be carried out using an appropriate conventional carbamate-forming procedure, for example treating an appropriately protected compound of formula (I) with a suitable chloroformate ester;
- (d) converting a group R^1 which represents an unsubstituted heterocyclyl group into a group R^1 which represents a heterocyclyl group substituted with an alkylaminocarbonyl or dialkylaminocarbonyl group; such a conversion may be carried out using an appropriate conventional urea-forming procedure, for example treating an appropriately protected compound of formula (I) with a suitable carbamate or carbamyl halide, and;
- (e) converting a group R^1 which represents an unsubstituted heterocyclyl group into a group R^1 which represents a heterocyclyl group substituted with an amido group; such a conversion may be carried out using an appropriate conventional aminocarbonylating procedure, for example treating an appropriately protected compound of formula (I) with 1,1'-carbonyldiimidazole followed by ammonia.

The above mentioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected, for example those methods discussed in standard reference texts of synthetic methodology such as *P J Kocienski, Protecting Groups, (1994), Thieme*.

For any of the hereinbefore described reactions or processes, conventional methods of heating and cooling may be employed, for example electric heating mantles and ice/salt baths respectively. Conventional methods of purification, for example crystallisation and column chromatography may be used as required.

Where appropriate individual isomeric forms of the compounds of formula (I) may be prepared as individual isomers using conventional procedures such as

the fractional crystallisation of diastereoisomeric derivatives or chiral high performance liquid chromatography (chiral HPLC).

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

The salts and solvates of the compounds of formula (I) may be prepared and isolated according to conventional procedures.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assay:

CCR-3 Binding Assay

A CCR-3 competition binding SPA (scintillation proximity assay) was used to assess the affinity of novel compounds for CCR-3. Membranes prepared from K562 cells stably expressing CCR-3 (2.5µg/well) were mixed with 0.25mg/well wheat-germ agglutinin SPA beads (Amersham) and incubated in binding buffer (HEPES 50 mM, CaCl₂ 1 mM, MgCl₂ 5 mM, 0.5% BSA) at 4°C for 1.5 hr. Following incubation, 20 pM of [¹²⁵I] eotaxin (Amersham) and increasing concentrations of compound (1pM to 30µM) were added and incubated in a 96 well plate for 2 hr at 22°C then counted on a Microbeta plate counter. The total assay volume was 100 µl. Competition binding data were analysed by fitting the data with a four parameter logistic equation. Data are presented as the mean pIC₅₀ values (negative logarithm of the concentration of compound which inhibits [¹²⁵I]eotaxin binding by 50%) from at least two experiments.

The compounds of the Examples were tested in the CCR-3 binding assay.

The compounds of the Examples tested in the CCR-3 binding assay possessed pIC₅₀ values in the range 7.3 – 8.1.

Examples of disease states in which the compounds of the invention have potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as bronchitis (including chronic bronchitis), bronchiectasis, asthma (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD), cystic fibrosis, sinusitis and rhinitis. Also included are diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure.

Furthermore, compounds of the invention may be used to treat nephritis; skin diseases such as psoriasis, eczema, allergic dermatitis and hypersensitivity reactions; and diseases of the central nervous system which have an inflammatory component (eg. Alzheimer's disease, meningitis, multiple sclerosis), HIV and AIDS dementia.

Compounds of the present invention may also be of use in the treatment of nasal polyposis, conjunctivitis or pruritis.

Further examples of disease states in which compounds of the invention have potentially beneficial effects include cardiovascular conditions such as atherosclerosis, peripheral vascular disease and idiopathic hypereosinophilic syndrome.

Compounds of the invention may be useful as immunosuppressive agents and so have use in the treatment of auto-immune diseases such as allograft tissue rejection after transplantation, rheumatoid arthritis and diabetes.

Compounds of the invention may also be useful in inhibiting metastasis.

Diseases of principal interest include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.

It will be appreciated by those skilled in the art that references herein to treatment or therapy extend to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful as therapeutic agents.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

There is also therefore provided a compound of formula (I), or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions, e.g. asthma or rhinitis.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of inflammatory conditions, eg. asthma or rhinitis.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject suffering from or susceptible to an inflammatory condition e.g. asthma or rhinitis, which method comprises administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way.

There is thus further provided a pharmaceutical composition comprising a compound of formula (I), or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

There is also provided a process for preparing such a pharmaceutical formulation which comprises admixing the compound of formula (I) or a

physiologically acceptable salt or solvate thereof with one or more physiologically acceptable diluents or carriers.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, parenteral or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl *p*- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multidose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically

into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

The compounds and pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example antihistaminic agents, anticholinergic agents, anti-inflammatory agents such as corticosteroids, e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide; or non-steroidal anti-inflammatory drugs (NSAIDs) eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, trypsin and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists; or beta adrenergic agents such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof; or anti-infective agents e.g. antibiotic agents and antiviral agents. It will be appreciated that when the compounds of the present invention are administered in combination with other therapeutic agents normally administered by the inhaled or intranasal route, that the resultant pharmaceutical composition may be administered by the inhaled or intranasal route.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.001 to 500mg/kg body weight, preferably 0.01 to 500mg/kg body weight, more preferably 0.01 to 100mg/kg body weight, and at any appropriate frequency e.g. 1 to 4 times daily. The precise dosing regimen will of course depend on factors such as the therapeutic indication, the age and condition of the patient, and the particular route of administration chosen.

Throughout the description and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The invention is illustrated by reference to, but is in no way limited by, the following Examples.

For the avoidance of doubt, the free bond on the R¹ groups as presented in the Tables signifies the point of attachment of the R¹ groups to the residue of the molecule.

It should be noted that, for clarity, compounds of the Descriptions and the Examples are referred to by number, for example "Description 3" and "Example 5". The structures of the Examples so referred to are given in Table 1.

General experimental details

Mass Directed Automated Preparative HPLC column, conditions and eluent

Mass directed automated preparative high performance liquid chromatography was carried out using an LCABZ+ 5 μ m (5cm x 10mm internal diameter) column, employing gradient elution using two solvent systems, (A) 0.1% formic acid in water, and (B) 95% acetonitrile and 0.5% formic acid in water, at a flow rate of 8ml min⁻¹. Mass spectrometry was carried out using a VG Platform Mass Spectrometer, with an HP1100 Diode Array Detector and Accurate Flow Splitter.

LC/MS System

The following Liquid Chromatography Mass Spectroscopy (LC/MS) System was used:

This system used an 3 μ m ABZ+PLUS (3.3cm x 4.6mm internal diameter) column, eluting with solvents: A – 0.1%v/v formic acid + 0.077% w/v ammonium acetate in water; and B – 95:5 acetonitrile:water + 0.05%v/v formic acid, at a flow rate of 3 ml per minute. The following gradient protocol was used: 100% A for 0.7mins; A+B mixtures, gradient profile 0 – 100% B over 3.5mins; hold at 100%B for 1.1mins; return to 100% A over 0.2mins.

The LC/MS system used a micromass spectrometer, with electrospray ionisation mode, positive and negative ion switching, mass range 80-1000 a.m.u.

Thermospray Mass Spectra

Thermospray Mass Spectra were determined on a HP 5989A engine mass spectrometer, +ve thermospray, source temperature 250°C, probe temperatures 120°C (stem), 190°C (tip), detection mass range 100-850 a.m.u. Compounds were injected in 10 μ l of a mixture of solvents comprising 65% methanol and 35% 0.05M aqueous ammonium acetate, at a flow rate of 0.7ml/min.

Solid phase extraction (ion exchange)

'SCX' refers to Isolute Flash SCX-2 sulphonic acid solid phase extraction cartridges.

All temperatures are in °C

Descriptions

Description 1: 2,2,2-Trifluoro-N-(morpholin-2-ylmethyl)acetamide

To a stirred solution of morpholin-2-ylmethylamine (3.1g) in methanol (70ml) under nitrogen was added an ethereal solution of ethyl- α,α,α -trifluoroacetate (5ml in 20ml ether) which had been washed with saturated aqueous sodium bicarbonate, water and brine, and dried. The mixture was stirred for 30 min at 22°C before removal of all volatiles in vacuo. The residue was dissolved in

methanol (10ml) and the volatiles again removed *in vacuo* to give the title compound as a white crunchy foam (4.9g).
Thermospray Mass Spectrum m/z 213 $[MH^+]$.

Description 2: N-([4-(3,4-Dichlorobenzyl)morpholin-2-yl]methyl)-2,2,2-trifluoroacetamide

To a stirred solution of Description 1 (3.3g) in N,N-dimethylformamide (50ml) under nitrogen was added potassium carbonate (2.46g) and sodium iodide (2.12g). A solution of 3,4-dichlorobenzyl chloride (2ml) in N,N-dimethylformamide (10ml) was added dropwise to the mixture. The mixture was stirred at 22°C for 18h before the volatiles were removed *in vacuo*. The residue was partitioned between dichloromethane (100ml) and saturated aqueous sodium carbonate solution (50ml). The organic phase was subsequently washed with additional saturated aqueous sodium carbonate solution (2 x 50ml) and water (50ml) before drying over magnesium sulphate, filtering and evaporation of the solvent *in vacuo* to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 25% ethyl acetate in cyclohexane, to give the title compound as a colourless oil (2.97g).
LC/MS R_t 2.63 min, Mass Spectrum m/z 371 $[MH^+]$.

Description 3: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine

To a stirred solution of Description 2 (2.97g) in methanol (15ml) and water (5ml) was added potassium carbonate (5.53g). The mixture was stirred at 22°C for 18h before the methanol was removed *in vacuo*. Water (25ml) was added and the mixture extracted with ethyl acetate (3 x 30ml). The combined organic phases were washed with water (5ml) and saturated aqueous sodium chloride solution (10ml) before drying over sodium sulphate, filtering and evaporation of the solvent *in vacuo* to give a pale yellow oil. The oil was purified by Biotage flash chromatography on a 90g silica cartridge eluting with 75:8:1 dichloromethane/ethanol/0.880 ammonia solution. The required fractions were combined and the solvent evaporated *in vacuo* to give the title compound as a colourless oil (1.85g).
LC/MS R_t 1.77 min, Mass Spectrum m/z 275 $[MH^+]$.

Description 4: [4-(3,4-Dichlorobenzyl)morpholin-2-yl]methylamine (alternative synthesis)

A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (Chem Abs No. 40172-06-3, 0.980g) and 2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (1.10g) was heated at 80°C under nitrogen for 3h. The resulting solid mass was treated with concentrated sulphuric acid (1.5ml) then stirred at 150°C for 24h. The mixture

was treated with water (100ml) then washed with ethyl acetate (2x100ml). The dark aqueous phase was basified to ~pH 12 using 5M aqueous sodium hydroxide, then extracted with ethyl acetate (2x100ml). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under vacuum to give the title compound as a brown oil (1.02g). Mass spec. m/z 275 (MH^+).

Description 5: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine

Description 3 (racemic mixture, 8g) was separated into its single enantiomers by preparative chiral-HPLC. The separation was carried out using a 2" x 22cm Chiralpak AD 20 μm column, Merck self pack DAC system, eluting with 95:5:0.1 (v/v) heptane : absolute ethanol: diethylamine (flow rate: 55ml/min over 40min, UV detection 225nm); sample load preparation: 400mg sample in 20ml 3:2 (v/v) absolute ethanol: system eluent.

The title compound (2.49g) was obtained as follows: preparative HPLC retention time 23.0 min.

Description 5 (Alternative procedure)

A slurry of Description 7 (1.00g) in water (8.5ml) was heated to 75° and then treated dropwise with concentrated sulphuric acid (2.5ml). The mixture was then heated at reflux. After 23h the reaction mixture was cooled to 22° and then treated with dichloromethane (6ml). 880 Ammonia solution (7ml) was then added dropwise with cooling. More dichloromethane (10ml) was added. The aqueous phase was separated and extracted with more dichloromethane (10ml). The combined organic phase was washed with water (5ml) and then evaporated to dryness. The residue was redissolved in dichloromethane and the solvent re-evaporated to give the product as an oil (662mg).

Description 6: 1-[(2S)-4-(3,4-Dichlorobenzyl)morpholin-2-yl]methanamine salt with D-tartaric acid 1:1

Description 3 (0.613g) was dissolved in methanol (12.3ml). D-Tartaric acid (0.335g) was added and the slurry was heated to reflux for 50min. The mixture was allowed to cool to 0-5°C and the precipitate isolated by filtration to give the title compound as a white solid (0.4g).

ee: 76%ee

Chiral analytical HPLC (Chiralpak AD column, 4.6 x 250mm, eluent 50:50:0.1 MeOH: EtOH: Butylamine, flow rate 0.5ml/min, UV detection at 220nm), Rt 8.9min.

Description 7: 2-[4-(3,4-Dichloro-benzyl)-morpholin-2-ylmethyl]-isoindole-1,3-dione

A mixture of 2-[(3,4-dichlorobenzyl)amino]ethanol (2.038 g) and (S)-2-(oxiran-2-ylmethyl)-1H-isoindole-1,3(2H)-dione (2.032g) in tetrahydrofuran (3.3ml) was stirred and heated at reflux under nitrogen. After 21.5h more tetrahydrofuran (12.5ml) was added and the mixture was cooled to 3°. Triphenyl phosphine (2.793g) was added and the mixture was stirred until all the solid had dissolved. Diisopropylazodicarboxylate (2.1ml) was then added over 12min maintaining the temperature at <7°. After 2.25h the mixture was allowed to warm to 22°. After 5.3h more triphenylphosphine (121mg) and diisopropylazodicarboxylate (0.09ml) were added. After 22.5h the reaction mixture was concentrated to near dryness. Propan-2-ol (12ml) was added and the concentration repeated, this was repeated once more. More propan-2-ol (12ml) was added and the mixture was heated to 70°. After 0.5h the slurry was cooled to 22° and then after a further 2h the product was collected. The bed was washed with propan-2-ol (2x4ml) and then dried in vacuo at 40° to give the product, (2.622g).

Description 8: 4-Nitrophenyl [4-(3,4-dichlorobenzyl)morpholin-2-yl]methylcarbamate

Triethylamine (0.09ml) was added to solution of Description 3 (0.150g, 0.545mmol) in dichloromethane (3ml) with stirring at 20°C under nitrogen. The solution was cooled to 0°C and a solution of 4-nitrophenyl chloroformate (0.121g) in dichloromethane (1ml) was added drop-wise. The resultant mixture was stirred for 4h at 0°C. The solution was allowed to warm to 20°C, washed with brine (4ml), dried (MgSO₄), and concentrated in vacuo. Purification by Biotage flash chromatography on silica gel, eluting with 35% ethyl acetate in cyclohexane, gave the title compound (0.2g).

LC-MS: Rt 3.1mins. Mass Spectrum *m/z* 441 [MH⁺].

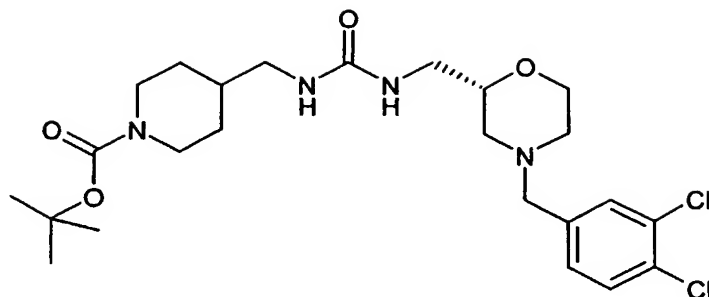
Description 9: 4-Nitrophenyl [(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methylcarbamate

Description 9 was prepared in an analogous manner to Description 8 from Description 5 (0.225g) and 4-nitrophenylchloroformate (0.182g) to yield the title compound (0.2g).

LC-MS Rt 3.1mins. Mass Spectrum *m/z* 441 [MH⁺].

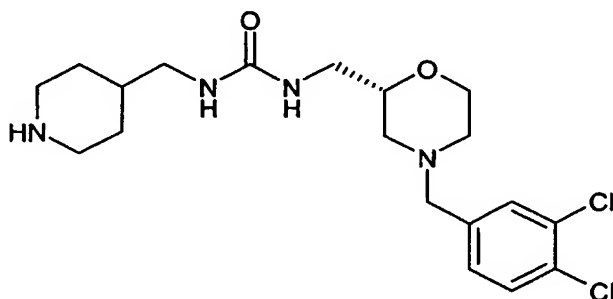
Examples

Synthetic Method A

Example 9

A solution of 4-aminomethyl-1-tert-butoxycarbonylpiperidine (0.235g) in dry dichloromethane (2ml) was added to a stirred solution of Description 9 (0.440g) and N,N-diisopropylethylamine (0.35ml) in dry dichloromethane (10ml) at 22° under nitrogen, and the mixture was stirred at 22° for 17h. The mixture was partitioned between dichloromethane (10ml) and 2N aqueous sodium hydroxide (3x20ml); the organic layers were washed with water (3x20ml), dried (MgSO₄) and evaporated in vacuo to give a pale yellow oil (0.60g). Purification by chromatography on silica gel (Varian Bondelut cartridge, 10g), eluting with dichloromethane: ethanol: 880 ammonia 100:0:0 - 95:5:0.5 (gradient elution), gave the title compound (0.460g).

LC/MS , Rt = 2.70min, Mass Spectrum m/z 515 [MH⁺]

Example 10

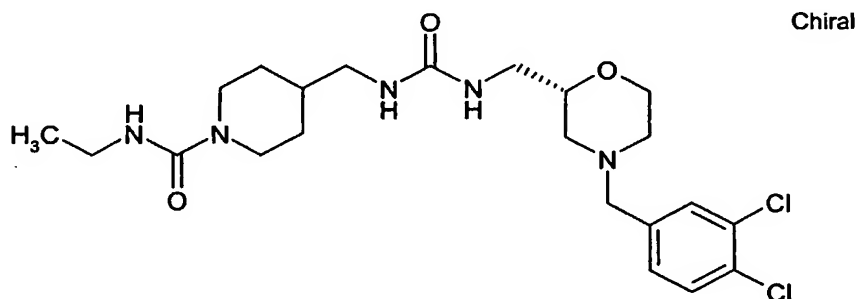
The compound of Example 9 was dissolved in dry 1,4-dioxane (6ml), and the stirred solution treated with 4M hydrogen chloride in 1,4-dioxane (6ml), giving a white precipitate. The mixture was stirred at room temperature for 16h, and the solvent was evaporated in vacuo to give the title compound hydrochloride as a white solid (0.518g).

LC/MS , Rt = 1.83min, Mass Spectrum m/z 415 [MH⁺]

The solid was dissolved in methanol and applied to an Isolute SCX ion exchange cartridge (10g, pretreated with methanol). Elution with methanol followed by 10% 880 ammonia in methanol, followed by evaporation of the methanol/ammonia fraction, gave the free base (0.221g).

Synthetic Method B

Example 1

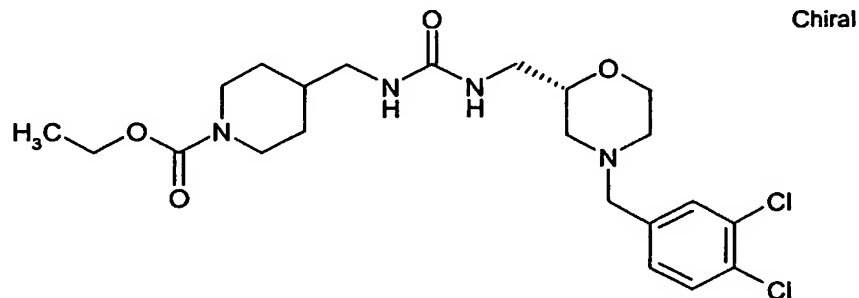


A solution of Example 10 (0.037g) in a mixture of dichloromethane (2ml) and N,N-dimethylformamide (0.5ml) was treated with ethyl isocyanate (0.008ml), and the mixture was stirred at 22° under nitrogen for 16h. The mixture was applied directly to an Isolute SCX ion exchange cartridge (2g, pretreated with methanol), and eluted with methanol followed by 10% 880 ammonia in methanol. Evaporation of the methanol/ammonia fraction gave a pale yellow gum (0.029g), which was purified by mass directed preparative HPLC to give the title compound (0.0147g).

LC/MS , Rt = 2.24min, Mass Spectrum m/z 486 [MH⁺]

Synthetic Method C

Example 3.



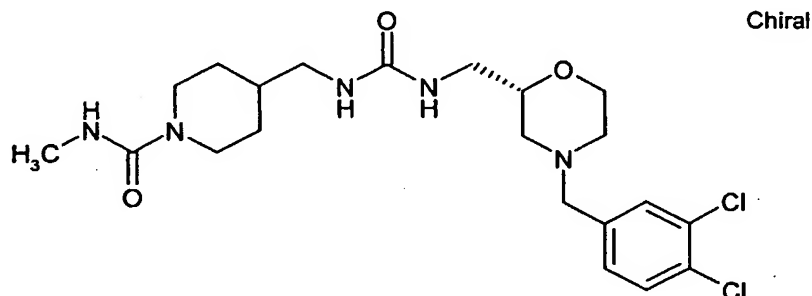
Ethyl chloroformate (0.0096ml) was added to a stirred solution of Example 10

(0.037g) and N,N-diisopropylethylamine (0.035ml) in dichloromethane (2ml) and N,N-dimethylformamide (0.5ml), and the mixture was stirred at 22° for 16h. The mixture was applied directly to an Isolute SCX ion exchange cartridge (2g, pretreated with methanol), and eluted with methanol followed by 10% 880 ammonia in methanol. Evaporation of the methanol/ammonia fraction gave a gum (0.026g), which was purified by mass directed preparative HPLC to give the title compound (0.0169g).

LC/MS , Rt = 2.50min, Mass Spectrum m/z 487 [MH⁺]

Synthetic Method D

Example 5

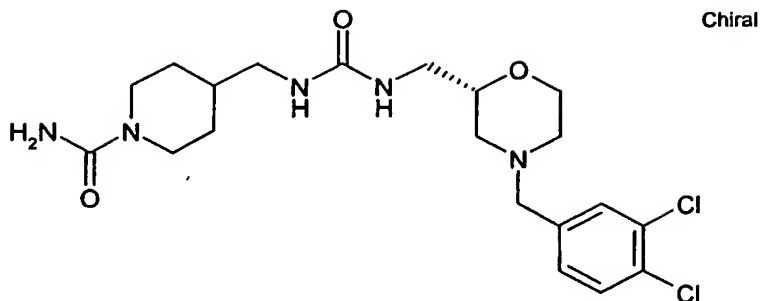


A solution of Example 10 (0.037g) and N,N-diisopropylethylamine (0.035ml) in dichloromethane (2ml) and N,N-dimethylformamide (0.5ml) was treated with 4-nitrophenyl N-methylcarbamate (Tetrahedron (1994), 50(34), 10367-70) (0.0195g), and the mixture was stirred at 22° under nitrogen for 16h. The mixture was applied directly to an Isolute SCX ion exchange cartridge (2g, pretreated with methanol), and eluted with methanol followed by 10% 880 ammonia in methanol. Evaporation of the methanol/ammonia fraction gave a pale yellow gum (0.024g), which was purified by mass directed preparative HPLC to give the title compound (0.0177g).

LC/MS , Rt = 2.21min, Mass Spectrum m/z 472 [MH⁺]

Synthetic Method E

Example 4

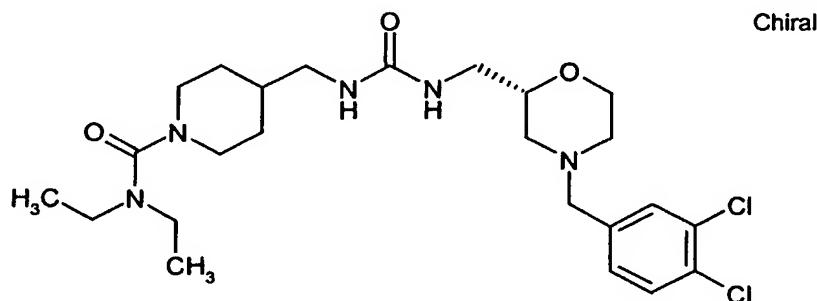


A solution of Example 10 (0.063g) in N,N-dimethylformamide (3ml) was added slowly to a solution of 1,1-carbonyldiimidazole (0.074g) in N,N-dimethylformamide (1ml) and the mixture was stirred under nitrogen at room temperature for 3 days. 0.880 Ammonia (2ml) was then added and stirring continued for a further five hours. A further portion of 0.880 ammonia (2ml) was added and stirring continued again for 16 hours after which time the solution was concentrated to dryness. 0.880 Ammonia was added, the solution heated at 50°C in a thick walled sealed vial (Reacti-vial™) for 3 hours then blown down to dryness. The residue was dissolved in methanol then loaded onto an SCX ion exchange cartridge, which had been pre-treated with methanol and which was then eluted with methanol and 10% .880 ammonia/methanol. Basic fractions were combined and concentrated to give a residue which was further purified on Biotage silica gel eluting with 92:7:1 dichloromethane:ethanol: 0.880 ammonia. Appropriate fractions were combined and concentrated in vacuo to give the title compound (0.027g) as a white solid.

LC/MS , Rt = 2.04min, Mass Spectrum m/z 458 [MH⁺]

Synthetic Method F

Example 6



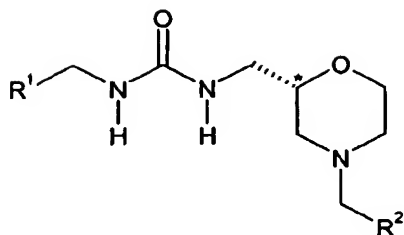
A solution of Example 10 (0.028g) in dichloromethane (1ml) and N,N-diisopropylethylamine (0.014ml) was treated with diethylcarbamyl chloride

(0.010ml) and the reaction stirred for 16 hours at room temperature. The solution was concentrated in vacuo, dissolved in methanol then loaded onto an SCX (1g) ion exchange cartridge, which had been pre-treated with methanol and which was then eluted with methanol and 10% 0.880 ammonia/methanol. Basic fractions were combined and concentrated to give the title compound (0.030g) as a clear gum.

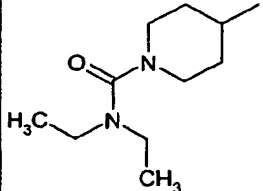
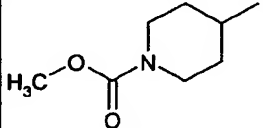
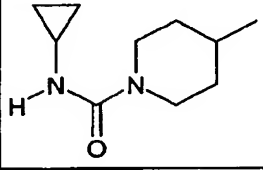
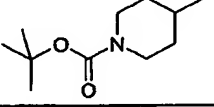
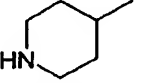
LC-MS , Rt = 2.55 min. Mass Spectrum m/z 514 [MH⁺]

The further examples described in the following Table were prepared according to or by analogy with the methods hereinbefore described.

Table 1



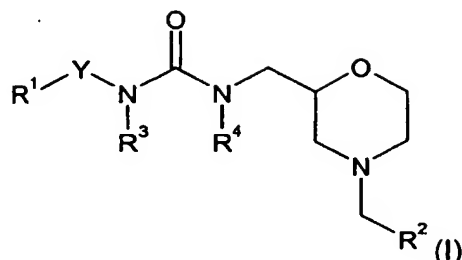
Ex. No.	Synthetic Method	R ¹	R ²	Stereochem at position (*)	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) [M+H] ⁺ of lowest mass isomer unless otherwise indicated
1*	B		3,4-di-ClPh	S	486.44	486
2*	B		3,4-di-ClPh	S	500.47	500
3	C		3,4-di-ClPh	S	487.431	487
4	E		3,4-di-ClPh	S	458.392	458
5*	D		3,4-di-ClPh	S	472.41	472

Ex. No.	Synthetic Method	R ¹	R ²	Stereochem at position (*)	Calculated Mol. Wt.	Observed Mol. Wt. (LC/MS) [M+H] ⁺ of lowest mass isomer unless otherwise indicated
6	F		3,4-di-ClPh	S	514.5	514
7*	C		3,4-di-ClPh	S	473.40	473
8*	D		3,4-di-ClPh	S	498.45	498
9	A		3,4-di-ClPh	S	515.48	515
10	A		3,4-di-ClPh	S	415.36	415

* Examples 1, 2, 5, 7, and 8 are formate salts

Claims

1. A compound of formula (I):



wherein:

R^1 represents substituted or unsubstituted heterocyclyl;

Y represents $-(CR_{na}R_{nb})_n-$;

R_{na} and R_{nb} are each independently hydrogen or C_{1-6} alkyl;

n is an integer from 1 to 5;

R^2 represents unsubstituted or substituted aryl or unsubstituted or substituted heteroaryl;

R^3 and R^4 each independently represent hydrogen or C_{1-6} alkyl;

and salts and solvates thereof;

with the proviso that the following compounds are excluded;

N-[[4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-[2-(2-oxoimidazolidin-1-yl)ethyl]urea;

tert-butyl 4-([4-(3,4-dichlorobenzyl)morpholin-2-yl]methylamino)carbonylamino)methyl)piperidine-1-carboxylate;

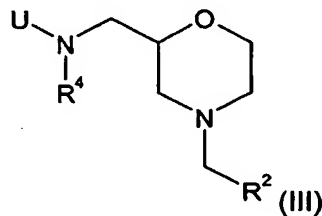
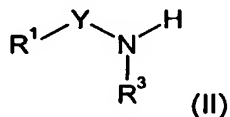
N-[[1-(cyclopropylcarbonyl)piperidin-4-yl]methyl]-N'-{[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl}urea, and;

N-[[[(2S)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]-N'-{[1-(methylsulfonyl)piperidin-4-yl]methyl}urea.

2. A compound of formula (I) according to claim 1 wherein R^1 is unsubstituted or substituted piperidinyl.

3. A compound of formula (I) according to claim 1 or claim 2 wherein R^1 is selected from 1-(methylaminocarbonyl)piperidin-4-yl, 1-(diethylaminocarbonyl)piperidin-4-yl, 1-(methoxycarbonyl)piperidin-4-yl, 1-(cyclopropylaminocarbonyl)piperidin-4-yl, 1-(ethylaminocarbonyl)piperidin-4-yl, 1-(iso-propylaminocarbonyl)piperidin-4-yl, 1-(ethoxycarbonyl)piperidin-4-yl, 1-(tert-butoxycarbonyl)piperidin-4-yl and 1-(aminocarbonyl)piperidin-4-yl.

4. A compound of formula (I) according to any one of the preceding claims wherein R_{na} and R_{nb} are both hydrogen.
5. A compound of formula (I) according to any one of the preceding claims wherein n is 1.
6. A compound of formula (I) according to any one of the preceding claims wherein R^3 and R^4 are both hydrogen.
7. A compound of formula (I) according to any one of the preceding claims wherein R^2 is unsubstituted or substituted phenyl.
8. A compound of formula (I) according to any one of the preceding claims wherein R^2 is phenyl substituted with chloro.
9. A compound of formula (I) according to any one of the preceding claims wherein R^2 is 3,4-dichlorophenyl.
10. A compound of formula (I) according to claim 1 selected from the Examples.
11. A compound of formula (I) according to claim 10 selected from Examples 1, 2, 3, 6, 4, 5, 7, and 8.
12. A compound of formula (I) according to claim 10 selected from Examples 1, 2, and 3.
13. A process for the preparation of a compound of formula (I) as defined in claim 1 which process comprises the reaction of a compound of formula (II) with a compound of formula (III);



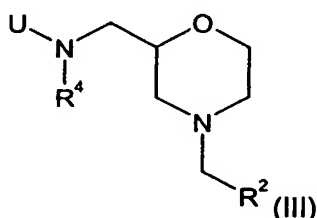
wherein;

R^1 , Y, R^3 , R^4 , and R^2 are as hereinbefore defined for formula (I) in claim 1 and U is a urea-forming group;

and thereafter, if required, carrying out one or more of the following optional steps:

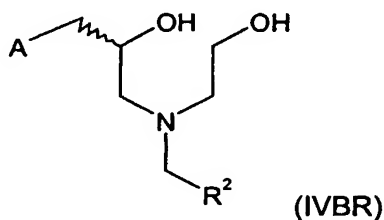
- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) removing any necessary protecting group;
- (iii) preparing a salt or solvate of the compound so formed.

14. A compound of formula (III)



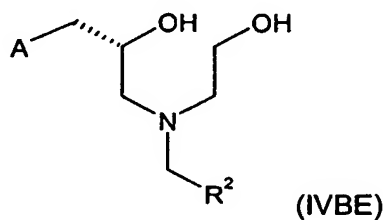
wherein U is a urea-forming group and R^2 and R^4 are as defined for formula (I) in claim 1.

15. A compound of formula (IVBR)



wherein A is a protected amino group and R^2 is as defined for formula (I) in claim 1.

16. A compound of formula (IVBE)



wherein A is a protected amino group and R^2 is as defined for formula (I) in claim 1.

17. A compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

18. A compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions, e.g. asthma or rhinitis.

19. Use of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of inflammatory conditions, eg. asthma or rhinitis.

20. A method for the treatment of a human or animal subject suffering from or susceptible to an inflammatory condition e.g. asthma or rhinitis, which method comprises administering an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof.

21. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/03349

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/5377 A61P29/00 A61P11/06 C07D413/12 C07D413/06
C07D209/48 C07D265/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 02 26723 A (HARRISON LEE ANDREW ; JUDD DUNCAN BRUCE (GB); GLAXO GROUP LTD (GB);) 4 April 2002 (2002-04-04) examples, intermediates 10, 13, 14 claims 1, 25	1-21
X	KATO S ET AL: "NOVEL BENZAMIDES AS SELECTIVE AND POTENT GASTRIC PROKINETIC AGENTS 1. SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF N-(2-MORPHOLINY)ALKYL BENZAMIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 33, no. 5, May 1990 (1990-05), pages 1406-1413, XP001037844 ISSN: 0022-2623 example 9	15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

7 July 2003

Date of mailing of the international search report

16/07/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Johnson, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/03349

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 31032 A (HOFFMANN LA ROCHE) 2 June 2000 (2000-06-02) page 2, line 25 - line 27; claim 1 -----	1-21

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 14-16 (part)

Claims 14-16 do not fulfil the requirements of Article 6 PCT because the matter for which protection is sought is not clearly defined. The terms "urea-forming group" and "protected amino group" do not enable the skilled man to determine which compounds are encompassed by these claims because the said groups can only be identified by knowing under what conditions and with which reagents a urea group is formed or an amino group remains protected. These conditions are not specified in these claims. The claims have therefore been searched according to the broadest definition in the description which does fulfil the requirements of clarity, namely compounds of claim 14 wherein U is imidazolylcarbonyl, chlorocarbonyl or 4-nitrophenoxy carbonyl (p. 7) and compounds of claims 15 and 16 wherein A is phthalimido (p. 8).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/03349

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 20 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 14-16 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/03349

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0226723	A	04-04-2002	AU 9014601 A	08-04-2002
			WO 0226723 A1	04-04-2002
			NO 20031443 A	26-05-2003
<hr/>				
WO 0031032	A	02-06-2000	AU 1382500 A	13-06-2000
			BR 9915520 A	17-07-2001
			CA 2350903 A1	02-06-2000
			CN 1331677 T	16-01-2002
			CZ 20011760 A3	12-12-2001
			DE 19955794 A1	31-05-2000
			WO 0031032 A1	02-06-2000
			EP 1131288 A1	12-09-2001
			ES 2158814 A1	01-09-2001
			FR 2786185 A1	26-05-2000
			GB 2343893 A , B	24-05-2000
			HU 0104364 A2	29-04-2002
			IT T0991009 A1	21-05-2001
			JP 2002530374 T	17-09-2002
			NO 20012411 A	16-05-2001
			PL 348375 A1	20-05-2002
			TR 200101398 T2	21-09-2001
			US 6166015 A	26-12-2000
<hr/>				